Extensive Absorption of 2',3'-Dideoxyinosine by Intratracheal Administration in Rats

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Purpose. To evaluate the intratracheal route of administration as an alternative to oral administration for 2',3'-dideoxyinosine (ddI).

Methods. A ddI dose (40 mg/kg/300 μl or 6.5 mg/kg/50 μl) was instilled into the trachea in female Fisher rats and an intravenous tracer dose (9 μg/kg) of ^{3}H-ddI was administered concomitantly to determine the drug clearance. Plasma concentrations were analyzed for the rate and extent of absorption.

Results. ddI was rapidly absorbed from the lungs, with a bioavailability of 63% at 40 mg/kg and 101% at 6.5 mg/kg. By comparison, our previous data showed an oral bioavailability of about 15% (Pharm Res., 9:822, 1992). The distribution of a dye solution instilled intratracheally showed that a fraction of the 300 μl dose spilled over to the gastrointestinal tract, where the entire 50 μl dose was retained in the lungs. The different distribution of the two doses/volumes likely contributed to the different bioavailability, with a fraction of the higher dose/volume degraded in the gastrointestinal tract after the spillover. Absorption of ddI from the airspace of the lung was biexponential, suggesting two absorption processes.

Conclusions. These data indicate significantly higher and less variable bioavailability of ddI by the intratracheal route of delivery compared to the oral route. Furthermore, the complete bioavailability at the lower dose/volume indicates no significant pulmonary first pass elimination for ddI.

KEY WORDS: drug therapy; AIDS; intratracheal intubation; biological availability; animal studies; 2',3'-dideoxyinosine.

INTRODUCTION

2',3'-Dideoxyinosine (ddI) is used for patients with acquired immunodeficiency syndrome. ddI inhibits the reverse transcriptase of the human immunodeficiency virus isolated from patients (1). Constant drug exposure is preferred for its antiviral activity (2). At present ddI is given to patients orally. However, ddI is acid labile, undergoes extensive gastrointestinal and hepatic first pass elimination, and oral administration results in variable bioavailabilities even after coadministration with antacids (3–6). Our laboratory has evaluated alternative noninvasive delivery routes, including the rectal and percutaneous administration routes (7–9). The rectal and percutaneous bioavailability of ddI in rats is between 15 to 30%, comparable to the oral bioavailability.

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The intrapulmonary route offers several advantages over the oral route. Drug delivery to the lung circumvents drug loss due to nonenzymatic and enzymatic degradation in the gastrointestinal tract and liver (10). The alveoli, in close contact with blood capillaries, provide a large absorption surface area that measures 50 to 100 m^2 in man (11). The nearly neutral lung pH of 6.2 to 7.4, with an apparent pH at the absorption site of 6.6 (12), offers an additional advantage for the delivery of acid-labile compounds such as ddI. The present study evaluated the systemic absorption of ddI after intratracheal administration and the effect of instillation volume on absorption kinetics.

MATERIALS AND METHODS

Chemicals. ddI (lot 234-B-1), [8-^{3}H] ddI (lot 5549-117; specific activity, 11.0 μCi/μg), and ftorafur [N1-(2-tetrahydrofuranyl)-5-fluorouracil] were obtained from the National Cancer Institute (Bethesda, Maryland). HPLC analysis showed that ddI and ftorafur were >98% pure. HPLC solvents were purchased from Sigma and Fisher Scientific (Cincinnati, Ohio). Ecolite scintillation cocktail was obtained from ICN Biochemicals (Costa Mesa, California). All chemicals and reagents were used as received.

Animal Protocol. Two groups of female Fisher rats, 5-6 months old, were housed in metabolic cages and had access to food and water ad lib. The pretreatment body weights of the rats for the two groups were 233.8 ± 15.4 g (mean ± SD, n = 6) and 236.3 ± 12.7 g (n = 6), respectively. ddI was administered intratracheally using previously published methods (13–15) with minor modifications. Briefly, one day before the study, a rat was anesthetized with intraperitoneal Avertine (1 ml/100 g body weight; 3.1% amyl alcohol and 12.5 mg/ml tribromoethanol in water), and a permanent catheter was implanted in the right jugular vein. The trachea between the cartilage rings located at 4 cm below the lower lip was punctured with a 25 G needle. A PE-10 tubing was inserted 2.5 cm deep into the trachea and the hole was sealed using one drop of Krazy Glue (Borden Inc., Columbus, Ohio). Animals were allowed to recover for at least 6 hr after surgery. Studies were performed on conscious animals. Dose administration was between 8 and 12 am. One group of rats received via intratracheal catheter a ddI dose of 40 mg/kg (about 300 μl), and the other group a dose of 6.5 mg/kg (about 50 μl). During the intratracheal instillation, no unusual behavior of the rats was observed. The intratracheal dose was followed 2–3 min later by an intravenous tracer dose of [^{3}H]ddI (100 μCi/kg or 9 μg/kg). The intravenous dose was administered over 10 sec and the intratracheal dose over 1 min. We found previously that the elimination of ddI was concentration dependent (16). In order to calculate the absolute intratracheal bioavailability, it was necessary to obtain the drug clearance by i.v. [^{3}H]ddI during the disposition of the intratracheal dose. The dosing solutions, containing 30 mg/ml ddI or 40 μCi/ml [^{3}H]ddI, were prepared in physiological saline and the pH adjusted to 7.0 with phosphoric acid and sodium hydroxide. The solutions were stored frozen. Under these conditions, less than 2.5% of ddI was degraded in one month. Beginning at 1.5 min after the administration of the intratracheal ddI dose, serial blood samples

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(200 μl) were withdrawn through the venous catheter and kept on ice to avoid drug degradation by blood enzymes (16). Plasma was obtained by centrifugation at 13,000 g and 0° C for 3 min. Urine was collected for 24 hr. Both plasma and urine samples were stored at −20°C until analysis within 1 week.

Distribution of an Aqueous Solution After Intratracheal Delivery. The distribution of an aqueous, neutral dye solution (0.2% trypan blue) in the lung, trachea, esophagus, tongue, stomach, and intestinal tract was studied in 15 additional rats. The tissue distribution was examined as a function of the instilled volume ranging from 50 to 350 μl. Ten min after intratracheal instillation of the dye solution, the animal was sacrificed, and a midsection incision was made from superior to the urethral orifice to inferior to the chin. The tissues of interest (lung, trachea, esophagus, tongue, stomach and intestines) were exposed, and the distribution of the dye was examined visually and graded for color intensity on a 4-point scale. A mean quasi-static lung volume of 22.7 mL/kg at 40 cm H_2O inflation pressure was reported for rats (17). Hence, the maximum instillation volume (350 μl) was about 7% of the quasi-static lung volume.

Sample Analysis. Plasma samples were analyzed as described elsewhere (18). In brief, 100 μl of plasma was mixed with 300 μl of 100 mM phosphate buffer, pH 6.9, and 100 μl of the internal standard, ftorafur (10 μg/100 μl). ddI and ftorafur were separated from polar endogenous compounds using solid phase extraction. Extracts were analyzed by HPLC using a reversed-phase μBondapak C_{18} column (Waters Associates, Milford, Massachusetts) and an aqueous mobile phase containing 10 mM sodium phosphate and 4% acetonitrile (18). UV detection was at a wavelength of 254 nm. Retention times of ddI and ftorafur were 5.1 and 7.8 min, at flow rate 2.0 ml/min, respectively. For the analysis of [^{3}H]ddI concentrations, HPLC-eluting fractions at 4.1 to 6.1 min were collected, and radioactivity was determined by liquid scintillation counting using a Packard 1600 TR scintillation counter (Meriden, Connecticut). The counting efficiency for ^{3}H was 45%. Plasma concentrations of [^{3}H]ddI were less than 0.1% of the total ddI concentrations at all times. Hence, the total ddI concentrations measured by UV absorbance were not corrected for the [^{3}H]ddI concentrations. The standard curves for [^{3}H]ddI quantitation were established from the ratio of the ddI radioactivity to the UV absorbance of the internal standard. Urine samples were diluted 10- to 100-fold, mixed with 100 mM phosphate buffer and ftorafur. The diluted urine mixture was analyzed by HPLC without extraction. The assay sensitivity limit was 100 ng/ml in plasma and in urine.

Determination of Intratracheal ddI Bioavailability. The ddI plasma concentration-time profiles were analyzed using standard pharmacokinetic methods, as described in previous publications (19,20). The area under the drug concentration-time curve (AUC), plasma clearance ($Clearance_{IV}$), volume of distribution at steady state (Vd_{SS}), mean residence time (MRT), and renal clearance were obtained by non-compartmental methods. Compartmental analysis with a two compartment open model, with elimination solely from the central compartment, was used to estimate the AUC from the time of administering the intravenous dose to the time of the first plasma sample at 0.5 min. Further parameters determined by compartmental methods included the volume of central compartment (V_1), and microconstants describing the drug transfer between the two compartments (k_{12} and k_{21}) and elimination from the central compartment (k_{10}).

The intratracheal bioavailability, F_{IT}, was determined from the plasma data according to Equation 1 and from the urine data according to Equation 2. Fe_{IV} and Fe_{IT} are the fractions of the intravenous and intratracheal doses excreted unchanged in urine in 24 hr.

$$F_{IT} = \frac{AUC_{IT} \times Clearance_{IV}}{Dose_{IT}} \quad (1)$$

$$F_{IT} = \frac{Fe_{IT}}{Fe_{IV}} \quad (2)$$

Analysis of Absorption Kinetics of Intratracheal ddI. The absorption of intratracheally administered ddI was evaluated by Loo-Riegelman equation using the software ABSPLOTS (21). The absorption profile suggested two absorption processes with different rate constants. The corresponding pharmacokinetic model is a two compartment open model with first order elimination and two absorption rates (Figure 1). The differential equations for the amounts in the central compartment (x_1) and in the peripheral compartment (x_2) are as follows:

$$\frac{dx_1}{dt} = k_{a1}A_1 + k_{a2}A_2 + k_{21}x_2 - (k_{12} + k_{10})x_1$$

$$\text{where } A_1 = F_{IT}Dose_1\, e^{-k_{a1}t} \quad (3)$$

$$A_2 = F_{IT}Dose_2\, e^{-k_{a2}t}$$

$$\frac{dx_2}{dt} = k_{12}x_1 - k_{21}x_2 \quad (4)$$

where F_{IT}Dose is the total bioavailable intratracheal dose, $F_{IT}Dose_1$ and $F_{IT}Dose_2$ are the amounts of ddI absorbed via the two absorption processes. Division of equation 3 by V_1 gives the changes in plasma concentration, C_p, with time:

$$\frac{dC_p}{dt} = k_{a1}F_{IT}\frac{Dose_1}{V_1}e^{-k_{a1}t} + k_{a2}F_{IT}\frac{Dose_2}{V_1}e^{-k_{a2}t} + k_{12}C_2 - (k_{12} + k_{10})C_p \quad (5)$$

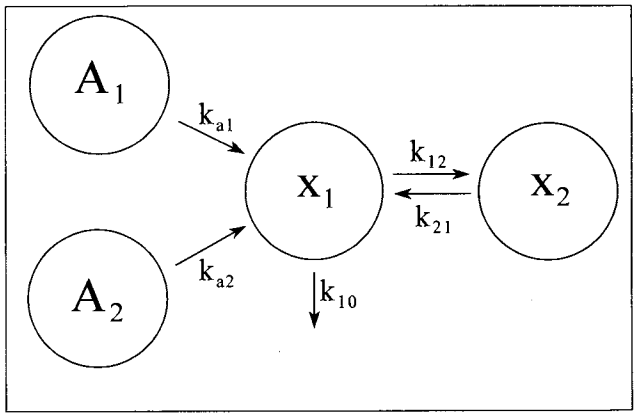

Fig. 1. Pharmacokinetic model. A two-compartment model with two absorption processes with different rate constants.

Table I. Distribution of Dye Solution After Intratracheal Instillation[a]

Volume (μl)	Upper right lung	Lower right lung	Upper left lung	Lower left lung	Trachea	Esophagus	Tongue	Stomach	Intestine
50	++++	−/+	−/+	−/+	+++	−	−	−	−
100	++++	−/+	−/+	−/+	+++	−	−	−	−
150	++++	+++	++	+	+++	++	++	+	++
250	++++	+++	+++	++	+++	+++	+++	++	+++
350	++++	+++	+++	++	++++	++++	++++	+++	++++

[a] Different volumes of a 0.2% trypan blue solution were instilled into the rat trachea. Three rats were used for each instillation volume. Ten minutes later, the animal was sacrificed and the dye distribution was examined visually. The dye intensity was graded visually from none (−) to most intense (++++).

For one absorption rate ($k_{a2} = 0$), the equations reduce to those published by Gilbaldi and Perrier (22).

Data fitting was done using PCNONLIN (SCI Software, Statistical Consultants Inc., Lexington, Kentucky). This program uses the Nelder-Mead least-squares regression analysis algorithm to determine the best-fit parameters (23). The coefficient of variation associated with concentration analysis was approximately constant, independent of concentration. Hence, the variance was proportional to C_p^2. A weighting function of $1/C_p^2$ was used to yield a weighted variance independent of concentration.

Statistical Analysis. Statistical analysis was done using the unpaired Student's t test and analysis of variance at a 5% level of significance. The goodness of fit for the methods with either one or two absorption rates were compared based on the randomness of scatter, and by using Akaike's Information Criterion (AIC), Schwartz Criterion (SC) (24) and coefficient of determination (r^2).

RESULTS

Distribution of an Aqueous Solution After Intratracheal Injection. Table I shows that the tissue distribution of a solution, containing trypan blue dye for visualization, was dependent on the instilled volume. For a volume ≥150 μl, the dye was found in lung, trachea, esophagus, tongue, stomach, and intestinal tract. For a smaller volume of ≤100 μl the dye was found only in the upper right lung and trachea, and was nearly invisible in the lower right lung and in the left lung. The distribution of dye solution in the lungs was heterogeneous. The upper part of the lung contained more dye than the lower part, and the right lung contained more than the left lung. This preferential distribution to the right lung is expected, since the connection between the trachea and the right main bronchus is straighter than the connection with the left main bronchus (25). Furthermore, the dye in the upper region of the lung was localized in several spots rather than uniformly spread. Based on these data, two instillation volumes, 50 μl and 300 μl, were selected for ddI administration, to determine the effect of instillation volume on intratracheal drug absorption.

Pharmacokinetics of Intravenous ddI. Figure 2 shows the plasma concentration-time profiles of the intravenously administered [^{3}H]ddI and Table II summarizes the pharmacokinetic parameters. Compared to the 6.5 mg/kg dose, the clearance and k_{10} after the 40 mg/kg dose were significantly lower and the $t_{1/2\alpha}$ and $t_{1/2\beta}$ values significantly higher. The lower clearance at the higher AUC indicates a nonlinear disposition of ddI in rats, consistent with our previous findings (16). Furthermore, the clearance obtained in the present

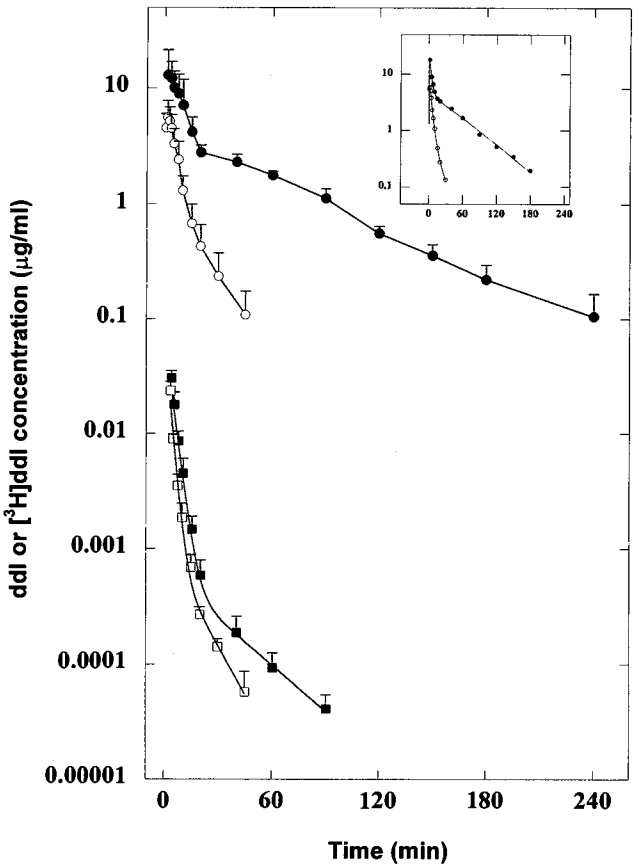

Fig. 2. Plasma concentration-time profiles of intratracheal ddI and intravenous [^{3}H]ddI. Intratracheal ddI was administered in doses of 40 mg/kg/300 μl or 6.5 mg/kg/50 μl. [^{3}H]ddI, 100 μCi/kg, was administered intravenously 2 to 3 min after administration of the two intratracheal ddI doses. [^{3}H]ddI was measured by HPLC fractionation and scintillation counting. Solid symbols: 40 mg/kg experiments; open symbols: 6.5 mg/kg experiments; circles: intratracheal ddI; squares: intravenous [^{3}H]ddI. The error bar indicates one S.D. Time zero is the time when the intratracheal dose was given. The insert shows ddI plasma concentrations after intratracheal administration in two individual animals for 40 mg/kg and 6.5 mg/kg doses, respectively. The solid lines are best-fit lines to a two compartment open model with first order output and two absorption sites.

Table II. Pharmacokinetic Parameters of [^{3}H]ddI[a]

Rat	Body weight (g)	Clearance (ml/min/kg)	Renal clearance (ml/min/kg)	Vdss (L/kg)	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)
Group 1, after 40 mg/kg/300 μl, n = 6						
Mean ± SD	234 ± 15.2	74.0 ± 12.6	19.8 ± 5.5	641 ± 227	2.36 ± 0.13	21.8 ± 5.7
Range	218–259	54.6–85.8	13.2–28.9	377–839	2.15–2.44	15.0–31.1
Group 2, after 6.5 mg/kg/50 μl, n = 6						
Mean ± SD	236 ± 12.7	133 ± 19.5	14.8 ± 5.5	802 ± 84.9	1.59 ± 0.35	13.5 ± 4.5
Range	223–241	112–160	8.2–23.9	676–909	1.13–1.94	9.8–22.2
p	0.6	0.0001	0.15	0.13	0.0005	0.019

Rat	V_1 (L/kg)	k_{10} (l/min)	k_{12} (l/min)	k_{21} (l/min)	MRT_{iv} (min)	AUC (μg min/ml)
Group 1, after 40 mg/kg/300 μl, n = 6						
Mean ± SD	357 ± 56.8	0.253 ± 0.020	0.037 ± 0.010	0.037 ± 0.013	8.19 ± 2.36	1.39 ± 0.27
Range	279–431	0.232–0.287	0.029–0.056	0.015–0.052	5.47–11.12	1.17–1.83
Group 2, after 6.5 mg/kg/50 μl, n = 6						
Mean ± SD	404 ± 69.4	0.373 ± 0.069	0.071 ± 0.037	0.068 ± 0.020	5.47 ± 0.50	0.747 ± 0.139
Range	323–500	0.299–0.473	0.035–0.120	0.035–0.092	4.87–6.10	0.542–0.896
p	0.12	0.01	0.18	0.14	0.013	0.00001

[a] A dose of [^{3}H]ddI (100 μCi/kg) was intravenously administered 2 or 3 min after the intratracheal ddI dose of 40 mg/kg/300 μl or 6.5 mg/kg/50 μl.

study at the 40 mg/kg dose is nearly identical to that found previously (16).

Pharmacokinetics of Intratracheal ddI. Table III shows the pharmacokinetic parameters of the intratracheally administered ddI. The maximum plasma concentration was achieved at about 3 min, indicating a rapid absorption. The terminal half-life of the 40 mg/kg dose was more than double that after the 6.5 mg/kg dose. Because the half-lives were determined in the same concentration range of 0.1 to 1 μg/ml (Figure 2), the different half-lives for the two doses exclude saturable drug clearance as the cause, and indicate that the terminal half-life after the 40 mg/kg dose is rate-limited by absorption from the trachea.

The bioavailability of the higher intratracheal dose was incomplete, whereas the bioavailability of the lower dose was complete. The bioavailability values calculated using plasma or urine data were identical. The mean residence time is about 6 fold longer for the higher dose, due to the slower elimination and slower absorption.

Absorption Kinetics of Intratracheal Dose. Loo-Riegelman analysis of the absorption of the intratracheal doses is shown in Figure 3. The rate of drug absorption declines in a biexponential manner, indicating two absorption processes. Analysis of data using input from two sites (Figure 1) provided good fits with randomly distributed residuals for the individual animals. Data of representative animals are included in Figure 2. A model with a single absorption site yielded a poor fit with a non-random distribution of residuals. Analysis using the Akaike Information Criterion, Schwartz Criterion, and coefficient of determination supported the choice of the model with two absorption processes. Table IV summarizes the data analysis using this model. About two-thirds of the bioavailable dose was absorbed via the k_{a2} absorption process for the 40 mg/kg/300 μl

Table III. Pharmacokinetic Parameters of ddI After Intratracheal Administration

	C_{max}[a] (μg/ml)	t_{max}[b] (min)	AUC_{IT} (μg min/ml)	$t_{1/2}$ (min)	F from plasma data (%)	Fe_{iv}[c] (%)	Fe_{IT}[d] (%)	F from renal data (%)	MRT_{IT}[e] (min)
Group 1, 40 mg/kg/300 μl, n = 6									
Mean ± SD	17.1 ± 6.6	3.4 ± 2.5	345 ± 41	47.0 ± 12.0	63.2 ± 7.7	26.7 ± 5.2	17.0 ± 4.6	62.8 ± 6.1	61 ± 7
Range	12.3–29.8	1.5–7.5	284–403	32.3–62.8	55.0–73.4	19.1–34.4	10.8–24.2	56.1–70.3	50–71
Group 2, 6.5 mg/kg/50 μl, n = 6									
Mean ± SD	7.4 ± 1.5	2.2 ± 0.9	50.1 ± 8.7	14.0 ± 4.2	101.1 ± 5.4	16.6 ± 2.6	16.6 ± 2.6	100.3 ± 4.5	10.4 ± 3.1
Range	5.4–9.3	1.5–3.0	34.9–65.9	10.6–22.2	92–106	13.3–20.5	13.1–20.9	93–105	6.4–14.5
p	0.0056	0.31	0.00001	0.0001	0.00001	0.03	0.42	0.00001	0.00001

[a] C_{max}, the maximum plasma concentration.
[b] t_{max}, the time at which C_{max} has been reached after intratracheal administration.
[c] Fe_{iv}, Fraction of the dose excreted in the urine after intravenous administration.
[d] Fe_{IT}, Fraction of the dose excreted in the urine after intratracheal administration.
[e] MRT_{IT}, mean residence time of intratracheal dose.

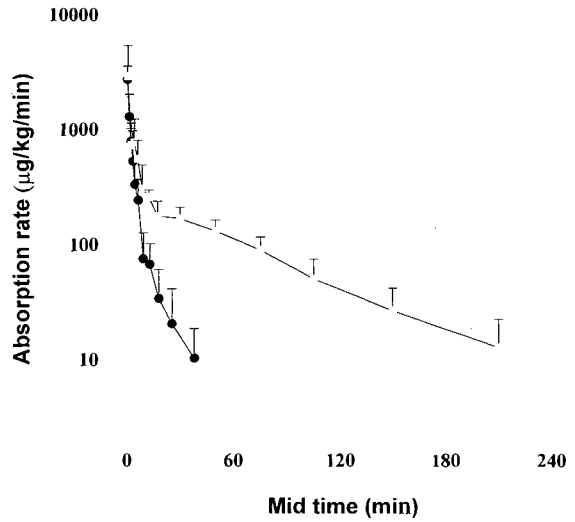

Fig. 3. Absorption profile of intratracheal ddI. The rate of absorption of ddI was analyzed by deconvolution. Solid symbols: 40 mg/kg experiments; open symbols: 6.5 mg/kg experiments.

dose group. For the 6.5 mg/kg/50 μl dose group, the k_{a1} absorption process was quantitatively more important and accounted for absorption of about two-thirds of the dose. The absorption from the first site was rapid with an average half-life of about 1.2 min for the high dose group and about 1.1 min for the lower dose group. The absorption from the second site was considerably slower with an average half-life of 43.3 min for the higher dose group and 8.5 min for the lower dose group. Among two dose groups, the difference in the k_{a2} was statistically significant, but the difference in the k_{a1} was not significant.

DISCUSSION

The first goal of this study was to explore the intratracheal delivery route as an alternative to the oral route for systemic delivery of ddI. The data show that the intratracheal bioavailability of ddI, calculated using either plasma or urine data, was about 63% for the 40 mg/kg/300 μl dose and 100% for the 6.5 mg/kg/50 μl dose. The dye distribution data show that a dose volume of ≤100 μl was localized in the right lung and trachea, whereas a volume of ≥150 μl led to spillage to the gastrointestinal tract. We infer from the dye distribution data that a fraction of the 40 mg/kg dose was transferred to the gastrointestinal tract where ddI was degraded, thus leading to the incomplete bioavailability. A similar spillage of ^{109}cadmium to the stomach after intratracheal administration has been reported (26). Compared to the 16% oral bioavailability of an unbuffered solution of ddI (40 mg/kg) in rats previously published by us (27), data of the present study show a superior systemic bioavailability and less interanimal variability for the intratracheal route. Furthermore, the 100% bioavailability for the 6.5 mg/kg dose indicates the absence of pulmonary first pass elimination of ddI.

The second goal was to examine the absorption kinetics of intratracheal ddI. The observed biexponential drug absorption indicates two absorption sites with different rate constants. This is because the other likely scenario, i.e., absorption from a single site with two absorption rates, would result in one apparent rate constant equal to the sum of the contributing rate constants, rather than two apparent rate constants. The presence of two or more sites of absorption is further suggested by our dye experiments showing distribution of instillate over various anatomical regions. The absorption rate constant for the second site was dependent on the administered dose and volume and were 5 fold higher for the 6.5 mg/kg/50 μl dose compared to the 40 mg/kg/300 μl dose. It is likely that k_{a1} and k_{a2}, as apparent absorption rate constants, reflect the absorption from multiple sites which may be grouped into two sites with rapid and slow absorption. Although the anatomical regions that comprise these different absorption sites are not known, the dye distribution data suggest the following. A higher volume of ≥150 μl was distributed, albeit to a different extent, in the four quadrants of the lungs, whereas a lower volume of ≤100 μl was localized in the upper right lung. The tracheal epithelium has been shown to have a ten-fold higher permeability for alpha-methyl-glucopyranoside (a nonmetabolizable analog of D-glucose) as compared to the alveolar epithelium (28). Localization of the drug in the upper part of the lung,

Table IV. Absorption Kinetics of Intratracheally Administered ddI[a]

	Deconvolution		Two-compartment model with two absorption sites					
	k_{a1} (min^{-1})	k_{a2} (min^{-1})	$F_{IT}DOSE_1$ (mg/kg)	$F_{IT}DOSE_2$ (mg/kg)	F_{a1} (%)	F_{a2} (%)	k_{a1} (min^{-1})	k_{a2} (min^{-1})
Group 1, 40 mg/kg/300 μl, n = 6								
Mean ± SD	0.61 ± 0.38	0.015 ± 0.005	7.90 ± 1.94	17.4 ± 2.86	31.3 ± 7.05	68.7 ± 7.05	0.60 ± 0.37[b]	0.016 ± 0.004
Range	0.16–0.94	0.009–0.020	5.23–11.0	13.2–21.8	23.0–39.8	60.2–77.0	0.16–0.92	0.011–0.021
Group 2, 6.5 mg/kg/50 μl, n = 6								
Mean ± SD	0.65 ± 0.31	0.075 ± 0.084	4.07 ± 1.14	2.49 ± 1.14	62.0 ± 17.4	38.0 ± 17.4	0.66 ± 0.29[b]	0.082 ± 0.086
Range	0.31–0.90	0.049–0.245	2.60–5.02	1.251–4.11	40.3–77.5	22.5–59.7	0.32–0.92	0.051–0.251
p	0.41	0.03	0.001	0.00001	0.0025	0.0025	0.40	0.032

[a] ddI plasma concentration-time profiles after an intratracheal dose were analyzed by deconvolution and using a two compartment model with two absorption sites.

[b] Estimation of k_{a1} was limited by the time of the first data point (1.5 min), and rate constants associated with an absorption $t_{1/2}$ of less than 0.75 min could not be estimated. Three animals in each group showed an absorption $t_{1/2}$ of less than 0.75 min. For these animals, k_{a1} was arbitrarily set equal to 0.92 min^{-1} (i.e., $0.693/t_{1/2}$).

i.e., the trachea and bronchi, may lead to a faster absorption rate than if the drug is localized in the lower part, i.e., the alveoli. This is supported by the 5 fold greater k_{a2} for the 6.5 mg/kg/50 μl dose that was localized in the upper respiratory tract, when compared to the 40 mg/kg/300 μl dose that was distributed to the upper and lower lungs as well as to the upper gastrointestinal tract. It is noted that the gastrointestinal tract was unlikely to be the second absorption site for the 40 mg/kg/300 μl, because the amount absorbed from the second site was 17.4 mg/kg, which is much greater than the calculated oral bioavailability of 6.4 mg/kg from the gastrointestinal tract (i.e., 16% of 40 mg/kg).

In conclusion, data of the present study indicate the intratracheal route as an attractive alternative to the oral route, and suggest at least two absorption sites in the lung for ddI. The intratracheal/intrapulmonary delivery may be further optimized by using appropriate dosing volumes and formulations that localize ddI distribution in the lungs, and by using sustained release formulations that provide constant drug concentrations which are preferred for the long-term antiviral effect of ddI.

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